

(19) World Intellectual Property Organization International Bureau



(43) International Publication Date  
31 December 2003 (31.12.2003)

PCT

(10) International Publication Number  
**WO 2004/000858 A3**

(51) International Patent Classification<sup>7</sup>: **A61K 31/70**, C07H 19/06, 19/10, 19/167, 19/20

(74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(21) International Application Number:  
**PCT/US2003/019172**

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(22) International Filing Date: 17 June 2003 (17.06.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/390,579 21 June 2002 (21.06.2002) US

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(71) Applicants (*for all designated States except US*): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). ISIS PHARMACEUTICALS, INC. [US/US]; 2292 Faraday Avenue, Carlsbad, CA 92008 (US).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): CARROLL, Steven, S. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). OLSEN, David, B. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). DURETTE, Philippe, L. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). BHAT, Balkrishen [IN/US]; 2292 Faraday Avenue, Carlsbad, CA 92008 (US). DANDE, Prasad [IN/US]; 2292 Faraday Avenue, Carlsbad, CA 92008 (US). ELDRUP, Anne, B. [DK/US]; 2292 Faraday Avenue, Carlsbad, CA 92008 (US).

**Published:**

- *with international search report*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:  
12 May 2005

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

WO 2004/000858 A3

(54) Title: NUCLEOSIDE DERIVATIVES AS INHIBITORS OF RNA-DEPENDENT RNA VIRAL POLYMERASE

(57) Abstract: The present invention provides nucleoside compounds and certain derivatives thereof which are inhibitors of RNA-dependent RNA viral polymerase. These compounds are inhibitors of RNA-dependent RNA viral replication and are useful for the treatment of RNA-dependent RNA viral infection. They are particularly useful as inhibitors of hepatitis C virus (HCV) NS5B polymerase, as inhibitors of HCV replication, and/or for the treatment of hepatitis C infection. The invention also describes pharmaceutical compositions containing such nucleoside compounds alone or in combination with other agents active against RNA-dependent RNA viral infection, in particular HCV infection. Also disclosed are methods of inhibiting RNA-dependent RNA polymerase, inhibiting RNA-dependent RNA viral replication, and/or treating RNA-dependent RNA viral infection with the nucleoside compounds of the present invention.

**INTERNATIONAL SEARCH REPORT**

International application No.

PCT/US03/19172

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) : A61K 31/70; C07H 19/06, 19/10, 19/167, 19/20  
 US CL : 514/45-51; 536/26.23, 26.26, 26.7, 26.74, 26.9, 27.6-27.63, 27.7, 27.8, 27.81, 28.5-28.55

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/45-51; 536/26.23, 26.26, 26.7, 26.74, 26.9, 27.6-27.63, 27.7, 27.8, 27.81, 28.5-28.55

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
 HCA Plus structure search

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE HCAPLUS, Chemical Abstracts, Vol. 139, Abstract No. 365176, HCA Plus Accession Number 2003:892793 (Columbus, Ohio, USA), WO 03/093290 A2 (GENELABS TECHNOLOGIES, INC.) 13 November 2003, HCA Plus Abstract supplied, see pages 3-4 of abstract.	1-16
X, P	WO 02/057287 A2 (MERCK & CO., INC.) 25 July 2002, see entire document.	1-16
X, P	WO 02/057425 A2 (MERCK & CO., INC.) 25 July 2002, see entire document.	1-16
X	WO 01/16379 A1 (MERCK & CO., INC.) 08 March 2001, see entire document.	1-16
X	LI ET AL. 2'-C-Branched Ribonucleotides. 2. Synthesis of 2'-C-beta-Trifluoromethyl Pyrimidine Ribonucleosides. Organic Letters. 08 March 2001, Vol. 3, Issue No. 7, pages 1025-1028, see entire document.	1, 7
X	DUNKEL ET AL. Synthesis of 2'-C-Difluoromethyl Substituted Nucleoside Analogs as Ribonucleoside Replacements in Hammerhead Ribozymes. Nucleosides & Nucleotides. 1995, Vol. 14, Issue Nos. 3-5, pages 799-801, see entire document.	1-3, 7

Further documents are listed in the continuation of Box C.  See patent family annex.

* Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier application or patent published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means		
"P" document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

02 March 2005 (02.03.2005)

Date of mailing of the international search report

17 MAR 2005

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US  
 Commissioner of Patents  
 P.O. Box 1450  
 Alexandria, Virginia 22313-1450

Faxsimile No. (703) 305-3230

Authorized officer

L. E. Crane

Telephone No. 571-272-1600